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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,756	05/25/2005	Andreas Bergmann	121778-04341933	4938

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EXAMINER	
GEBREYESUS, KAGNEW H	
ART UNIT	PAPER NUMBER
1656	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,756	BERGMANN ET AL.	
	Examiner	Art Unit	
	Kagnew H. Gebreyesus	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10/19/04* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/25/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Priority

Priority is acknowledged for this application, which is the National Phase application of International Application No. PCT/EP2003/003939, filed April 15, 2003, which designates the United States. In addition this application claims foreign priority from European application Serial No. 020088415 under 35 U.S.C. § 365, filed on April 19, 2002.

Information Disclosure Statement

The information disclosure statement filed on May 25, 2005 has been considered as shown by the Examiners signature next to each reference.

Oath/Declaration

The oath or declaration submitted on May 25 2005 has been reviewed and is in compliance with 37 CFR 1.97 and 1.98.

Specification

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.

(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-17 are rejected under 35 U.S.C. 101 because the claimed recitation of a use or a method, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1-17 provides for the use of CPS 1 or an inhibitor thereof, but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 14 is rejected because of the terms CA 19-9, CA 125, S100B, S100A protein, CYFRA 21, TPS, CHP, LASP-1. These terms must be written in full in the first instance of their appearance.

Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 10 is indefinite in the recitation of "fragments which contain at least 2 amino acid partial sequences according to SEQ ID NO: 1-5 and SEQ ID NOs: 7 and 8. It is unclear as to whether the term should be interpreted as the "fragments" are at least two of the recited sequences or if the "fragments" comprise "at least two amino acids" of the recited sequences. It is suggested that applicants clarify the meaning of the term. In the interest of advancing prosecution the examiner has

applied the broader interpretation, i.e. the fragments contain (i.e. comprise) at least two amino acids of the recited sequences.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are directed to the use of CPS 1 and fragments thereof for diagnosis and prognosis of sepsis or inflammation or the use of CPS 1 inhibitors as encompassed by the claims. The claims are directed to the use of a genus of CPS 1 molecules and fragments optionally defined by molecular weight (6, 9) or N-terminal part or fragments of any size (1-5, 7, 8, 11-17) are directed to the use of a genus of CPS1 inhibitors having any structure from any source. In addition claim 17 is for diagnosis/prognosis of essentially any condition. The specification teaches the structure of a human CPS 1 of SEQ ID NO: 6 and specific fragments of SEQ ID NO: 6, i.e., SEQ ID NO: 1-5 (identified from the baboon sequence) or SEQ ID NO: 7 and 8 that can be used in the claimed method. However, the specification fails to describe the use of any other CPS 1 from any other biological source by any identifying characteristic or property other than the functionality of being a

CPS 1 enzyme or fragment thereof for the diagnosis and for the prognosis of any condition (such as a liver disease) other than for sepsis induced by infection. Furthermore the specification does not teach even a single species of inhibitor of CPS 1 to be used for preparation of any medicaments.

The court of appeals for the Federal Circuit has held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as structure, formula [or] chemical name, 'of the claimed subject matter sufficient to distinguish it from other material. " For claims drawn to a genus, MPEP § 2163 states the written description required for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by a disclosure of relevant identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification discloses only SEQ ID NO: 1-5, 7 and 8 as representative species of the recited genus of CPS 1 polypeptides or fragment thereof of to be used and fails to disclose even a single species of a CPS-1 inhibitor. In this case the genus of CPS 1 polypeptides encompasses widely variant species including those polypeptides from any source and any fragments thereof. The genus of CPS1 inhibitors encompasses widely variant species, including small molecules, proteins and nucleic acids, for

example. Other than noted disclosed representative species, the specification fails to describe a representative number of species of CPS1 or fragments thereof or inhibitors of any CPS1 by any identifying characteristics or properties other than the functionality of being a carbamoyl synthetase polypeptide (CSP1) or an inhibitor thereof. In addition the specification does not describe the use of any CPS 1 for the diagnosis and for the prognosis of any condition (such as a liver disease) other than for sepsis resulting from infection. While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus", it also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved without disclosing a representative number of species within the genus." In the instant case the recited genus of CPS 1 polypeptides encompass species widely variant with respect to their structures, which include polypeptides from any source having carbamoyl phosphate synthase activity (claims 1, 4, 6, 7, 9, 11-16) or any N-terminal portion of the CPS 1 of SEQ ID NO: 6 (claims 2, 3, 5, 8). In addition the specification also encompasses the use of any inhibitor of CPS 1 (17). As such, the disclosure of a method that uses a single polypeptide species of CPS 1 of SEQ ID NO: 6 or specific fragments of SEQ ID NO: 6 i.e. SEQ ID NO: 1-5, 7 and 8 is insufficient to be representative of the attributes and features of all CPS 1 species from any biological source as encompassed by the claimed genus of polypeptides for methods of diagnosis/prognosis of any condition as encompassed by the claims. In addition the specification does not teach an inhibitor for any CPS 1.

Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claim 1-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of human carbamoyl phosphate synthase of SEQ ID NO: 6 and specific fragments of SEQ ID NO: 6 as a marker for the diagnosis of sepsis in a biological fluid of a patient by using antibodies raised against the specific peptides of SEQ ID NO: 7 or 8, does not provide enablement for the: 1) use of any CPS 1 or fragment thereof of any size (such as short amino acid stretches such as 6 amino acids) from any biological source as a marker for the diagnosis and prognosis and for assessment of severity of sepsis or inflammatory diseases in connection to liver failure. 2) Use of any CPS-1 inhibitor (17) as broadly encompassed by the claims.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988). The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill

of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claims also encompasses the use of any CPS 1 from any biological source having any structure (claims 1, 4, 6, 7, 9, 11-17) or the use of any N-terminal part of the CPS 1 of SEQ ID NO: 6 of any size as a marker for use in the method of claims 1 or 7. The specification provides guidance and examples for the use of the CPS 1 of SEQ ID NO: 6 or soluble fragments of CPS 1 i.e. SEQ ID NO: 7 and 8, (page 26 under the sub-title: "CPS 1 immunoreactivity determinations in human plasmas of healthy normal persons and patients suffering from sepsis") to produce antibodies which are subsequently used to identify CPS 1 in the diagnosis of sepsis.

However, the specification does not teach the specific structure of any other CPS 1 from all possible biological sources (any animal) or the use of any N-terminal portion of the CPS 1 including SEQ ID NO: 6, wherein the number of amino acid residues is undefined, because amino acid stretches identical to short fragments within SEQ ID NO: 6 are likely to be found in unrelated polypeptide sequences and the results obtained using such fragments will be unpredictable. Also, while the specification provides guidance for using SEQ ID NO: 6, 7 and 8 for diagnosing sepsis, it is highly unpredictable as to whether SEQ ID NO: 6, 7, 8 can be used for diagnosing/prognosing any condition as broadly encompassed by the claims. For instance Tabuchi et al show than the level of CPS1 is not affected in liver of LPS treated rats up to 24 hrs post treatment. Thus Tabuchi et al's teaching shows the unpredictability of measuring CPS1 levels from any source over any given period of time for the diagnosis of sepsis. The

standard for meeting the enablement requirement is whether one of skill in the art can make the invention without undue experimentation. The amount of experimentation to make the claimed invention is enormous and undue.

Such experimentation entails identifying CPS 1 from any biological source having any structure or using any N-terminal portion of at least 2 amino acids for use as marker for the diagnosis and prognosis and for assessment of severity and subsequent courses of treatment and monitoring of a broad scope of conditions in a biological fluid. The specification does not provide sufficient guidance to enable one of skill in the art to determine those amino acid fragments of any size and structure from the N-terminal part of CPS 1 as claimed that can be used in the method because short amino acid stretches are likely to be found in unrelated polypeptide sequences and the results obtained using such fragments will be unpredictable. Thus, searching for the specific biological source and sequence/structure of CPS 1 from any source (claims 1, 4, 6, 7, 9, 11-17), or any N-terminal fragment of SEQ ID NO: 6 of any size (such as short amino acid stretches such as 2 amino acids) to be used in the method of claim 1 or claim 7 in connection with diagnosing or prognosing the broad scope of diseases in any organism is well outside the realm of routine experimentation.

The Examiner finds that one skilled in the art would require additional guidance, such as information regarding the specific amino acid sequence of the CPS 1 and/or fragment used, the organism in which the method is practiced, the amino acid sequence used to raise the antibody used to detect the particular CPS 1 and guidance on how the results obtained from the use of CPS 1 as a marker for the diagnosis and the prognosis

and monitoring of sepsis can be predictive for the use of CPS 1 as a marker for the diagnosis and the prognosis and monitoring of any condition broadly encompassed by the claims, e.g. liver failure. Without such guidance, the experimentation left to those skilled in the art is undue.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4, 7 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Ozaki et al. (Enzyme-Linked Immunosorbent Assay of Carbamoyl phosphate Synthase 1: Plasma Enzyme in Rat Experimental Hepatitis and Clearance. Enzyme protein 1994 95:48:213-221). Ozaki et al disclose that in galactosamine-induced rat hepatitis, plasma concentration of CPS 1 that was 1-2 µg/ml blood before the treatment, increased up to 125 µg/ml blood in 24 hr after the treatment and decreased back to control levels at 72 hrs (see abstract and page 215 results section). As stated above claims 1, 4, 7 and 11 as broadly interpreted encompass the use of CPS 1 levels or fragment thereof from any source to be used for the diagnosis, prognosis of inflammation in liver diseases. Thus the teachings of Ozaki et al that discloses enhancement of CPS 1 in experimental hepatitis would anticipate claims 1, 4, 7 and 11 in the instant application.

Claims 7, 11, 12 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Tabuchi et al (Regulation of Genes for inducible Nitric Oxide Synthase and Urea Cycle Enzymes in Rat Liver in Endotoxin Shock). Tabuchi et al disclose measuring the amount of protein and mRNA for CPS1 in LPS-treated rats. In addition they disclose measuring protein and mRNA of other urea cycle enzymes in LPS-treated rates at 24 hrs. The reference makes the conclusion that LPS does not affect protein but affects mRNA levels of CPS1 over a 24-hour period. See p. 222, Figure 2, page 223 fig. 3 left column. Thus claims 7, 11, 12 and 13 reciting a method of differential diagnosis and detection for the prognosis and assessment and severity and for the therapy-accompanying monitoring of sepsis and severe infection by determination of CPS 1 mRNA levels is anticipated by the disclosure of Tabuchi et al.

Claim 17 is rejected under 35 U.S.C. 102(b) as being anticipated by Cerdan et al. (Role of calcium as an inhibitor of carbamoyl phosphate synthetase I). Cerdan et al teach inhibition of rat liver CPS 1 activity in the presence of Ca^{2+}. Applicants claim 17 is drawn to the CPS 1 inhibitors with the intended use, "the preparation of a medicament for the treatment of sepsis and severe liver diseases". Thus Cerdan et al's disclosure is within the limitation of claim 17.

Relevant references: Yin et al. (Participation of different cell types in the restitutive response of the rat liver to periportal injury induced by allyl alcohol Journal of Hepatology 1999; 31: 497-507).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kagnew H. Gebreyesus whose telephone number is

571-272-2937. The examiner can normally be reached on 8:30 am-5: 30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Examiner: Kagnew Gebreyesus PhD.

Jan. 24, 2007

DAVID J. STEADMAN, PH.D.
PRIMARY EXAMINER